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Office of Surveillance and Epidemiology

Drug Use Review

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Subject: Lo Loestrin® Fe Drug Utilization Review

Drug Name(s):   Lo Loestrin® Fe (norethindrone acetate/ethinyl
                                  estradiol/ferrous fumarate tablets)

Application Type/Number: NDA 22-501

Applicant/sponsor: Warner Chilcott

OSE RCM #:   2012-905

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CONTENTS

EXECUTIVE SUMMARY

This review examines drug utilization patterns for Lo Loestrin® Fe (norethindrone acetate/ethinyl estradiol/ferrous fumarate tablets) in the pediatric population stratified by patient age 0-13, 14-17 years, and adults 18 years or older from October 1, 2010 through March 31, 2012.

- Lo Loestrin® Fe was the fifth most frequently dispensed medication out of the selected market, accounting for approximately 5% of the market during the review period.

- Approximately 978,500 prescriptions and approximately 336,000 patients received a dispensed prescription for Lo Loestrin® Fe from October 2010 through March 2012.

- Lo Loestrin® Fe prescriptions dispensed to the pediatric population (age 0-17 years) accounted for 113,000 prescriptions and 39,500 patients (12% of total prescriptions and patients) for the entire review period.

- Obstetrics/Gynecology (Ob/Gyn) was the top prescribing specialty for Lo Loestrin® Fe.

- According to U.S. office-based physician practices, "Dysmenorrhea" (ICD-9 625.3) was the only diagnosis code associated with the use of Lo Loestrin® Fe during the review period for pediatric patients aged 14-17 years. No drug use mentions were recorded in pediatric patients aged 0-13 years for the review period.

1   INTRODUCTION

The Office of Pediatric Therapeutics (OPT), and Pediatric and Maternal Health Staff (PMHS) have requested a review of drug utilization patterns for Lo Loestrin® Fe in preparation for mandatory safety reporting under the Pediatric Research Equity Act (PREA) at the September 2012 Pediatric Advisory Committee Meeting. The drug utilization data are requested to provide background and context for discussions at the advisory committee meetings. Using the currently available proprietary drug utilization databases, this review describes outpatient retail pharmacy utilization for Lo Loestrin® Fe from October 1, 2010 through March 31, 2012.

1.1   BACKGROUND

Lo Loestrin® Fe (norethindrone acetate/ethinyl estradiol/ferrous fumarate) is an oral combined hormonal contraceptive approved for marketing on October 21, 2010 under NDA 22-501. It is indicated for use by women to prevent pregnancy.[1]

1.2   PEDIATRIC USE

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[1] Lo Loestrin® Fe prescribing information http://www.loloestrin.com/index.jsp

Safety and efficacy of Lo Loestrin Fe have been established in women of reproductive age. Safety and efficacy are expected to be the same in post-pubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

2   METHODS AND MATERIALS

2.1   DETERMINING SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for Lo Loestrin® Fe. Sales data for year 2011 indicated that approximately 89% of packages (Eaches) were distributed to outpatient retail pharmacies; 8% were to mail order pharmacies; and 3% were to non-retail settings.[2] As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail order nor non-retail settings data were included in this analysis.

2.2   DATA SOURCES USED

Proprietary drug use databases were used to conduct this analysis (see Appendix 2 for full data descriptions).

IMS, Vector One®: National (VONA) was used to obtain estimates of the number of outpatient dispensed prescriptions for Lo Loestrin® Fe, stratified by patient age (0-13, 14-17, 18+ years), from October 2010 to March 2012. IMS, Vector One®: Total Patient Tracker (TPT) was used to obtain estimates of the number of patients receiving a dispensed prescription for Lo Loestrin® Fe, stratified by patient age (0-13, 14-17, 18+ years), in the outpatient setting from October 2010 to March 2012. Diagnoses associated with the use of Lo Loestrin® Fe, stratified by patient age (0-13, 14-17, 18+ years), were obtained from the Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel from October 2010 to March 2012.

2.3   PRODUCTS INCLUDED

For comparative purposes, other norethindrone acetate-containing contraceptive products with ferrous fumarate were also examined: Loestrin 24 Fe, Junel Fe, Microgestin Fe, Glidess Fe, Tilia Fe, Tri-Legest Fe, Loestrin Fe, and Estrostep Fe.

3   RESULTS

3.1   OUTPATIENT DISPENSED PRESCRIPTIONS FOR LO LOESTRIN® FE

Table 1 in Appendix 1 shows the nationally estimated number of dispensed prescriptions for Lo Loestrin® Fe and other contraceptive products containing norethindrone acetate with ferrous fumarate by patient age and product (0-13, 14-17, 18+ years) from U.S. outpatient retail pharmacies, October 2010 through March 2012. During the examined time, approximately 19 million prescriptions were dispensed for the selected market.

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[2] IMS Health, IMS National Sales Perspectives™. Year 2011. Extracted June 2012. File: NSPC 2012-905 Lo Loestrin Fe 6-25-12.xls

Loestrin 24 Fe (norethindrone acetate 1 mg/ethinyl estradiol 0.02 mg/ferrous sulfate 75 mg) was the most commonly dispensed agent at 49% (9.4 million prescriptions) of total prescriptions followed by Junel Fe 1/20 and Microgestin Fe 1/20 (norethindrone acetate 1 mg/ethinyl estradiol 0.02 mg/ferrous sulfate 75 mg) at 18% (3.4 million prescriptions) and 12% (2.35 million prescriptions), respectively. Lo Loestrin® Fe ranked fifth among the selected market, accounting for approximately 5% (978,500 prescriptions) of the selected market during the examined time.

From October 2010 through March 2012, approximately 866,000 prescriptions of Lo Loestrin® Fe were dispensed to adults aged 18 years or older. Of the Lo Loestrin® Fe prescriptions dispensed to pediatric patients, the majority, approximately 94% (106,000 prescriptions), were dispensed to patients aged 14-17 year and 6% (7,200 prescriptions) were dispensed to patients aged 0-13 years.

3.2 PATIENT UTILIZATION OF LO LOESTRIN® FE BY AGE

Table 2 in Appendix 1 shows the nationally estimated number of patients for Lo Loestrin® Fe by patient age (0-13, 14-17, 18+ years) from U.S. outpatient retail pharmacies, October 2010 through March 2012. During the examined time, approximately 336,000 patients received a dispensed prescription for Lo Loestrin® Fe. Adults 18 years or older accounted for approximately 299,000 Lo Loestrin® Fe patients. Of the pediatric patients with a dispensed prescription of Lo Loestrin® Fe, the majority, approximately 94% (37,000 patients), were dispensed to patients aged 14-17 year and 6% (2,800 patients) were dispensed to patients aged 0-13 years.

3.3 LO LOESTRIN® FE UTILIZATION BY PRESCRIBING SPECIALTY

Obstetrics/Gynecology (Ob/Gyn) was the top prescribing specialty for Lo Loestrin® Fe accounting for 74% (723,000 prescriptions) of prescriptions dispensed followed by Nurse Practioner (NP) at approximately 13% of prescriptions dispensed (122,000 prescriptions). Pediatricians accounted for approximately <1% (6,800 prescriptions) of prescriptions dispensed over the entire review period (*Table 3 in Appendix 1*).

3.4 DIAGNOSIS ASSOCIATED WITH THE USE OF LO LOESTRIN® FE BY PATIENT AGE

Diagnoses associated with the use of Lo Loestrin® Fe stratified by patient age were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were calculated for the estimates (*Table 4 in Appendix 1*).[3] For patients aged 18 years and older, approximately 38% of drug use mentions for Lo Loestrin® Fe were associated with the health care encounter code of "Contracep Mgmt-Counsel" (V250.0) and 20% of drug use mentions were associated with health care encounter code "Contracept Surveillance" (V254.0) during the study period. "Dysmenorrhea" (ICD-9 625.3) was the only diagnosis code for pediatric patients aged

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[3] Encuity Research, LLC. uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

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14-17 years, however, the number of mentions was below the acceptable count allowable to provide a reliable estimate of national use and should therefore be interpreted with caution. No drug use mentions were recorded for pediatric patients aged 0-13 years.

4   DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Lo Loestrin® Fe was distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. We focused our analysis on only the outpatient retail pharmacy setting, therefore, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order).

Indications for use were obtained using Encuity Research, LLC.'s PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Encuity Research, LLC. recommends caution when interpreting nationally projected estimates of annual uses or mentions that fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5   CONCLUSIONS

Among pediatric patients aged 0-17 years, Lo Loestrin® Fe accounted for 12% (113,000 prescriptions and 39,500 patients) of total Lo Loestrin® Fe prescriptions and patients during the examined time. Total Lo Loestrin® Fe prescriptions dispensed ranked fifth overall for the selected market during the review period.

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6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

Table 1. Nationally estimated number of dispensed prescriptions for contraceptive products containing norethindrone acetate and ferrous fumarate by patient age (ages 0-13, 14-17, 18+) in U.S. outpatient retail pharmacies, October 2010-March 2012

	10/2010-03/2012	
	TRx	**Share**
	N	**%**
Total Market	**19,255,719**	**100.0%**
Loestrin 24 Fe	**9,484,026**	**49.3%**
Age 0-13 yrs	31,637	0.3%
Age 14-17 yrs	861,962	9.1%
18+ yrs	8,589,279	90.6%
Unknown Age	1,147	0.0%
Junel FE	**3,427,847**	**17.8%**
Age 0-13 yrs	12,876	0.4%
Age 14-17 yrs	290,659	8.5%
18+ yrs	3,124,307	91.1%
Unknown Age	5	0.0%
Microgestin Fe 1/20	**2,351,162**	**12.2%**
Age 0-13 yrs	8,451	0.4%
Age 14-17 yrs	187,889	8.0%
18+ yrs	2,154,784	91.6%
Unknown Age	38	0.0%
Microgestn Fe 1.5/30	**1,510,934**	**7.8%**
Age 0-13 yrs	3,888	0.3%
Age 14-17 yrs	99,698	6.6%
18+ yrs	1,407,290	93.1%
Unknown Age	59	0.0%
Lo Loestrin Fe	**978,565**	**5.1%**
Age 0-13 yrs	7,211	0.7%
Age 14-17 yrs	105,619	10.8%
18+ yrs	865,734	88.5%
Unknown Age	1	0.0%
Gildess FE	**667,242**	**3.5%**
Age 0-13 yrs	3,408	0.5%
Age 14-17 yrs	62,695	9.4%
18+ yrs	601,140	90.1%
Tilia Fe	**363,909**	**1.9%**
Age 0-13 yrs	452	0.1%
Age 14-17 yrs	7,934	2.2%
18+ yrs	355,522	97.7%
Unknown Age	1	0.0%
Tri-Legest Fe	**324,386**	**1.7%**
Age 0-13 yrs	250	0.1%
Age 14-17 yrs	8,713	2.7%
18+ yrs	315,423	97.2%
Loestrin Fe 1/20	**76,532**	**0.4%**
Age 0-13 yrs	172	0.2%
Age 14-17 yrs	4,131	5.4%
18+ yrs	72,230	94.4%
Estrostep Fe	**71,039**	**0.4%**
Age 0-13 yrs	37	0.1%
Age 14-17 yrs	802	1.1%
18+ yrs	70,200	98.8%
All Others	**77**	**0.0%**

Source: IMS Vector One®: National, October 2010-March 2012
Data Extracted June 2012. File: VONA_2012-905_ Lo_ Loestrin_ Fe_market_by_age_6-25-12(1).xls

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Table 2. Nationally estimated number of patients (ages 0-13, 14-17, 18+) who filled a prescription for Lo Loestrin Fe in U.S. outpatient retail pharmacies, October 2010-March 2012

	10/2010-03/2012	
	Patient Count	Share
	N	%
Lo Loestrin Fe	335,953	100.0%
Age 0 - 13 yrs	2,820	0.8%
Age 14 - 17 yrs	37,211	11.1%
Age 18+ yrs	299,229	89.1%
Unknown Age	1	0.0%

Source: IMS Total Patient Tracker. Sep 2010-Mar 2012 Data Extracted June 2012 File: TPT 2012-905 Lo Loestrin Fe by age 6-5-12

Table 3. Nationally estimated number of dispensed prescriptions for Lo Loestrin Fe in outpatient retail pharmacies by top 10 prescribing specialties, October 2010-March 2012

	10/2010-03/2012	
	TRxs	Share
	N	%
Lo Loestrin Fe	978,565	100.0%
OB/GYN	722,824	73.9%
NP	122,163	12.5%
UNSPEC	39,641	4.1%
PA	28,650	2.9%
GP/FM/DO	28,386	2.9%
IM	8,342	0.9%
PED	6,759	0.7%
OTHER	3,731	0.4%
ENDO	3,024	0.3%
HOSP	2,720	0.3%
All Others	12,326	1.3%

Source: IMS Vector One® National, Oct 2010-Mar 2012 Data Extracted June 2012. File: VONA 2012-915 Lo Loestrin Fe by MD 6-5-12
*GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

Table 4. Diagnoses associated with the use* of Lo Loestrin Fe by patient age (0-13, 14-17, 18+) as reported by office-based physician practices, October 2010-March 2012

	10/2010-03/2012		
	Uses (000)	95% Confidence Interval Uses (000)	Share%
Lo Loestrin Fe	**1,548**	**1,362-1,734**	***100.0%***
Age 0-13 yrs		**no data return**	
Age 14-17 yrs	**11**	**<0.5-27**	***0.7%***
6253 DYSMENORRHEA	11	<0.5-27	*100.0%*
18+ yrs	**1,479**	**1,297-1,660**	***95.5%***
V250 CONTRACEP MGMT-COUNSEL	566	453-678	*38.3%*
V254 CONTRACEPT SURVEILLANCE	291	211-372	*19.7%*
V723 GYNECOLOGIC EXAMINATION	232	160-304	*15.7%*
6264 IRREGULAR MENSTRUATION	71	31-111	*4.8%*
V242 ROUT POSTPART FOLLOW-UP	70	30-109	*4.7%*
6253 DYSMENORRHEA	53	18-87	*3.6%*
2189 UTERINE LEIOMYOMA NOS	40	10-70	*2.7%*
6262 EXCESSIVE MENSTRUATION	31	5-57	*2.1%*
2564 POLYCYSTIC OVARIES	18	<0.5-39	*1.3%*
All Others	106	57-155	*7.2%*
UNSPEC	58	22-94	*3.8%*
V250 CONTRACEP MGMT-COUNSEL	22	<0.5-45	*38.6%*
V723 GYNECOLOGIC EXAMINATION	19	<0.5-40	*32.9%*
V254 CONTRACEPT SURVEILLANCE	14	<0.5-31	*23.4%*
7061 ACNE NEC	3	<0.5-11	*5.2%*

Source: Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel, Oct 2010-Mar 2012 Extracted June 2012. File: PDDA 2012-915 Lo Loestrin Fe by AgeDx4 6-5-12

* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

Note: Encuity recommends caution interpreting national estimates of drug uses below 100,000 as the sample size is very small with corresponding large confidence intervals

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6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

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Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA)

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

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